Four Year Follow Up of Fatigue in a Geographically-Defined Primary Biliary Cirrhosis Patient Cohort

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ABSTRACT

Background & Aims: Fatigue is the commonest symptom described by patients in most populations with the autoimmune liver disease primary biliary cirrhosis (PBC), and appears to be unrelated to liver disease severity. At present it is unclear how the fatigue experienced by patients (only characterised to date in cross-sectional studies) evolves over time. In this study we set out to address how fatigue had changed over 4 years of follow-up in a geographically defined cohort of PBC patient who participated in an earlier cross-sectional study of fatigue impact.

Methods: Participants in the original 2000 study who were still alive in 2004 were asked to complete the same fatigue assessment tool (FIS). In those who had died between 2000 and 2004 medical notes, death certificates and primary care records were reviewed.

Results: 108 of the original cohort of 136 patients were alive at the time of the follow-up study, 99 of whom (92%) participated in the follow-up study. With the exception of 4 patients who underwent transplantation between 2000 and 2004, all of whom showed significant improvement in fatigue severity as assessed by FIS, fatigue severity was unchanged over 4 years of follow-up. Amongst the 28 patients who died during the follow-up period survival was significantly lower in the patients who were fatigued at the 2000 baseline (FIS above the median for the whole PBC population (40/160)) (Log-Rank Test p=0.006 v non-fatigued at baseline patients). Increased fatigue severity was independently associated with decreased survival on multi-variate analysis. Fatigued PBC subjects were significantly more likely to have suffered a cardiac death than non-fatigued patients.

Conclusions: The fatigue phenotype appears to be highly stable in PBC. The presence of fatigue in PBC is independently associated with significantly increased risk of death in general and cardiac death in particular. The factors underpinning fatigue in PBC, and the mechanisms whereby fatigue is associated with increased mortality, warrant further study.
INTRODUCTION
Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with an autoimmune aetiology. Studies performed in UK,[3][4] Canadian,[5][6] USA [7][8] and French [9] populations have suggested that the condition is frequently characterised by profound fatigue which can often dramatically reduce patient quality of life.[10] The severity of the fatigue experienced by UK PBC patients is significantly greater than that experienced by age- and sex-matched chronic disease and community controls. [3][4] A recent small study based on a principally Scandinavian cohort did not, in contrast, identify significant fatigue in PBC patients suggesting the possibility of population variation in symptom penetrance.[11] In contrast to PBC-associated pruritus, where significant recent progress has been made in understanding symptom pathogenesis and in optimising treatment,[12] PBC-associated fatigue remains largely resistant to treatment,[13] although this is an area of active ongoing investigation.[14][15] The limited studies performed to date in PBC and in animal models of cholestasis regarding fatigue pathogenesis have suggested a significant role for centrally-mediated processes. [16][17][18][19] Studies of the disease associations of fatigue in PBC have shown universal agreement that, in contrast to pruritus, the severity of fatigue experienced by PBC patients shows no relationship to any conventional parameter of liver disease severity, suggesting that fatigue may be less a direct result of liver pathology and more an independent manifestation of PBC as a systemic disease.[5][6][3]

All studies addressing fatigue in PBC published to date have been cross-sectional in nature. It is, therefore, unclear how the impact of fatigue on individual patients changes over time. Indeed, it is not even clear whether the subgroup of patients experiencing fatigue (which ranges from 30 to 80% of all patients depending on the population studied and the quantification approach used) is static or whether all patients experience fatigue some of the time. Furthermore there is little information as to the relationship between the symptom of fatigue and prognosis. The aim of this study was to address the question of how fatigue changes over time in PBC, and to study the effects on clinical outcome of high and low fatigue states by performing follow-up assessment of a representative group of PBC patients originally studied in 2000.[4] This group of patients constituted a comprehensive, unselected cohort of PBC patients defined by geography, and was identified specifically to allow us to study fatigue severity in a meaningful patient cohort not biased by clinic attendance frequency.

SUBJECTS AND METHODS
The study cohort consisted of 136 patients defined by residence within the geographical area NE1-NE25 (Newcastle-upon-Tyne and surrounding suburbs) who participated in a previous study of fatigue and its impact in PBC.[4] The median FIS for this population was 40 (maximum possible 160). For the purposes of this follow-up study patients with an FIS \( \geq 40 \) at the study outset were defined as the high fatigue group and FIS<40 the low fatigue group. The rationale for studying this patient population, and the methods used to identify the study population have previously been described.[4] At the time of initial study all patients were asked to complete a symptom assessment tool that determined self-perceived health status and also contained the Fatigue Impact Score (FIS), previously validated as a fatigue assessment tool for self-completion use in English speaking PBC patients.[3][6] Patients also completed a detailed questionnaire addressing any other health problems that they were experiencing, and the medications that they were receiving. Pruritus severity was assessed using a visual analogue scale (VAS). For the follow-up study, patients were sent the same symptom and health assessment tool. Where patients had died comprehensive additional information regarding clinical events prior to death was gathered from hospital records, primary health care records and death certificates to supplement the study documentation. Using a previously adopted approach for cause of death assignation,[20] two of the investigators (JN and NB) examined all case documentation for each patient who died and independently ascribed the principal cause of death. Agreement regarding cause was present for all cases. The investigators who ascribed principal cause of death from the case documentation were blinded at the time as to the fatigue status at study enrolment of the patients who died. The design adopted for the control arm of the original cohort study, which included full anonymisation of controls subjects, precluded us from performing a follow-
up study of the control subjects. Ethical approval for this study was granted by the local research ethics committee.

**Statistical Analysis**

Survival following the original cohort study was compared in fatigued and non-fatigued patients using the Log-Rank Test. Proportions of fatigued and non-fatigued patients suffering cardiac death were compared using Fishers Exact Test. Cox proportional hazards regression was performed using SPSS to assess whether any association between fatigue scores and survival was independent of other clinical variables. Comparisons of biological parameters at enrolment between fatigued and non-fatigued patients who subsequently died on follow-up, and of FIS values at enrolment and follow-up were by parametric and non-parametric t-test as appropriate for the nature of the population value distributions. Proportions of patients in relevant subgroups were compared using Fishers Exact Test.

**RESULTS**

**Study Cohort**

Of the original cohort of 136 patients 28 (21%) died between the initial and follow-up assessments. Detailed clinical records were available for all these patients. Of the 108 survivors from the original cohort 99 (92%) participated in the follow-up study. Patient demographic clinical and laboratory data are given in Table 1. Four of the surviving patients and none of the non-survivors had undergone liver transplantation between initial assessment and follow-up.

**Table 1:** Demographic data for patients at the study outset. [4] Amongst the patients from the original cohort who were alive at follow-up (n=108) data are only given for those who agreed to participate in the follow-up element of the study (n=99, 92%). Unless otherwise indicated data are presented as median and [range]. na denotes not applicable

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>All Patients</th>
<th>Patients Alive at Follow-Up</th>
<th>Patients Dead at Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 [21-88]</td>
<td>62 [21-88]</td>
<td>77 [53-86]</td>
</tr>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>8 [3-131]</td>
<td>8 [3-131]</td>
<td>10 [4-69]</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42 [28-51]</td>
<td>42 [28-51]</td>
<td>40 [35.5-45]</td>
</tr>
<tr>
<td>Definite Disease (number [%])</td>
<td>81 [64]</td>
<td>62 [63]</td>
<td>19 [68]</td>
</tr>
<tr>
<td>Probable Disease (number [%])</td>
<td>46 [36]</td>
<td>37 [37]</td>
<td>9 [32]</td>
</tr>
<tr>
<td>Pruritus Present at Enrolment (number [%])</td>
<td>84 [62]</td>
<td>64 [59]</td>
<td>20 [71]</td>
</tr>
<tr>
<td>FIS at Enrolment (number [%])</td>
<td>40.5 [0-138]</td>
<td>35.5 [0-136]</td>
<td>54.5 [2-138]</td>
</tr>
<tr>
<td>FIS at FU (number [%])</td>
<td>na</td>
<td>37.5 [0-142]</td>
<td>na</td>
</tr>
<tr>
<td>Female (number [%])</td>
<td>116 [91]</td>
<td>90 [91]</td>
<td>26 [93]</td>
</tr>
</tbody>
</table>

**Subjects Surviving to Follow-Up**

Amongst the 95 surviving, non-transplanted patients fatigue severity as assessed by the FIS was unchanged after the 4 year follow-up period (Fig 1a & b). Significant change in fatigue score status.
amongst individual patients over the follow-up period was limited to the four patients who underwent transplantation, all of whom reported significant improvements in their FIS score (Fig 1b & c). Ursodeoxycholic acid (UDCA) usage appeared to have no detectable effect on fatigue severity (within the constraints of the study methodology) as no significant change in FIS was seen between 2000 and 2004 in patients not receiving UDCA at any point during the study period (Fig 2a), in patients who commenced UDCA at standard doses (12-15g/Kg/day) between 2000 and 2004 (Fig 2b) and in patients receiving UDCA throughout the study period (Fig 2c).

**Subjects Not Surviving to Follow-Up**
The patients who died during follow-up had higher FIS values at the study outset (median FIS 54.5 [range 2-138]) than the patients who survived to follow-up and who participated in the follow-up arm of the study (median FIS 35.5 [0-136], p<0.05, Fig 3a). 20/28 (71%) of the patients dying during follow-up had high fatigue scores at study outset (defined as FIS values above the median value for the whole PBC population (>40)) compared with 8/28 (29%) with low fatigue scores (defined as FIS values of FIS<40), p<0.005. By contrast, proportions of surviving and non-surviving patients with pruritus at the study outset (VAS >0) were similar (Table 1, p=ns). Survival over the study follow-up period was significantly lower by Kaplan-Meier analysis for the high fatigue patients at the study outset than for the low fatigue patients (Fig 3b). Presence of pruritus was, in contrast, not associated with significantly decreased survival by Kaplan-Meier analysis (data not shown). The association between a high fatigue score (FIS>40) at the study outset and risk of mortality on follow-up was independent of other, well established PBC prognosis associated variables (age, bilirubin and albumin which were found, along with FIS, to be associated with prognosis in this cohort on univariate analysis (data not shown)) and on Cox proportional hazard regression analysis (Table 2).

**Table 2:** Baseline biological parameters showing significant associations with subsequent survival on proportional hazards regression.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE(B)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIS</td>
<td>0.91</td>
<td>0.43</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>0.095</td>
<td>0.023</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.095</td>
<td>0.045</td>
<td>0.04</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.027</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

No association was seen between age or any parameter of liver disease severity (including serum albumin, bilirubin and PT) and fatigue severity in the whole study cohort at enrolment.[4] This observation remained true in retrospect for the group who went on to die during follow-up (Table 3). Moreover, the vast majority of patients in both the fatigued and non-fatigued groups at study outset who died during follow-up had normal liver synthetic function (Table 3). In terms of more general parameters of health, no correlation was also seen between self-reported general health status (which patients were asked to distinguish from fatigue), numbers of medications received blood glucose and TSH levels and fatigue severity at the study outset in the subjects who died during follow-up (Table 3).
Table 3: Baseline biological parameters and frequencies of abnormal values for key parameters and fatigue associated diagnoses in patients with high (FIS >40) and low (FIS<40) fatigue scores at study enrolment who died during follow-up. Health perception scores was a self-reported score of general health with values ranging from 1 (very poor health) to 4 (very good health). Subjects completing this scale were asked to consider the aspects of their health other than their fatigue. Number of medications received relates to prescription medications.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FIS&gt;40 n=20</th>
<th>FIS&lt;40 n=8</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/l)</td>
<td>40 [36-45]</td>
<td>38 [35.5-42]</td>
<td>ns</td>
</tr>
<tr>
<td>(n [%] albumin &lt;35g/l)</td>
<td>(0 [0])</td>
<td>(0 [0])</td>
<td>ns</td>
</tr>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>12 [4-69]</td>
<td>10 [8-47]</td>
<td>ns</td>
</tr>
<tr>
<td>(n [%] bilirubin &gt;17 µmol/l)</td>
<td>(3 [15])</td>
<td>(1 [12.5])</td>
<td>ns</td>
</tr>
<tr>
<td>(n [%] PT &gt;15sec)</td>
<td>(0 [0])</td>
<td>(2 [25])</td>
<td>ns</td>
</tr>
<tr>
<td>TSH (mu/l)</td>
<td>2.3 [0.5-3.8]</td>
<td>1.7 [1.2-2.8]</td>
<td>ns</td>
</tr>
<tr>
<td>(n [%] diagnosed thyroid disease)</td>
<td>(1 [5])</td>
<td>(1 [12.5])</td>
<td>ns</td>
</tr>
<tr>
<td>Random Blood Glucose (mmol/l)</td>
<td>7.0 [4.4-9.0]</td>
<td>8.0 [4.4-9.1]</td>
<td>ns</td>
</tr>
<tr>
<td>(n [%] diagnosed Type II DM)</td>
<td>(2 [10])</td>
<td>(0 [0])</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>75 [54-86]</td>
<td>71 [53-86]</td>
<td>Ns</td>
</tr>
<tr>
<td>Health Perception Score (1-4)</td>
<td>2 [1-4]</td>
<td>2 [1-3]</td>
<td>Ns</td>
</tr>
<tr>
<td>Numbers of Medications Received</td>
<td>2 [0-5]</td>
<td>2 [0-6]</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Despite the independent association between both albumin and bilirubin at enrolment and subsequent survival, liver disease was attributed as a direct cause of death in only 4 patients (variceal bleed n=2 & liver failure in 2). In contrast, 9 died of histologically confirmed malignant disease (carcinoma of the bronchus (n=3), oesophagus (n=2), breast (n=1) colon (n=1) and pancreas (n=1) and non-Hodgkin’s lymphoma (n=1). Of the remaining 15 patients 2 died of respiratory system sepsis not directly linked to liver disease (ie not following endoscopic procedures) and 13 were ascribed a cardiac cause of death (sudden cardiac events occurring in the absence of previous symptoms (all investigated with post-mortem) n=5, myocardial infarction n=5 and heart failure n=3). A principally cardiac cause of death was seen significantly more frequently seen in the group of patients with high outset fatigue scores who died during follow-up (12/20, 60%) than in the group of patients with low outset fatigue scores who died during follow-up (1/8, 12.5%, p<0.05).

DISCUSSION

In this study we set out to explore how the impact of fatigue evolves over time in PBC. The study population was a well-characterised and representative cohort of patients, defined by geography of residence, who had participated in an earlier study of fatigue impact in PBC.[4] The follow-up assessment reported in the current study took place 4 years after the original assessment. Full follow-up information was available for 93% of the original study cohort (99 subjects who were alive and participated in the follow-up study and 28 who had died during the follow-up period).

Fatigue severity as determined by FIS was unchanged in 2000 compared to 2004 amongst the patients not undergoing liver transplantation during follow-up. One potential explanation for this finding would be that the FIS lacks the responsiveness [21] to detect change in fatigue severity over time. The observations that the FIS had sufficient responsiveness to detect statistically significant improvement in fatigue severity in the small number of patients who did undergo liver transplantation in the follow-up phase of this study, and that the FIS has been demonstrated to be able to detect significant changes in fatigue severity in response to therapy in other disease settings,[22][23] would argue against this interpretation. The alternative explanation for the stability of the FIS over time, and the one which we favour, is that little or no change in fatigue severity in fact occurred over the time-period of the study. The conventional view to date in PBC has been that the condition goes through an initial asymptomatic phase which is followed by symptom development and, in due course, by the development of progressive disease.[24][25][26][27][28] If our interpretation is correct our
observations would challenge this view. The findings of the current study suggest that patients fall into fatigued and non-fatigued groups which, at least over 4 years, remain stable. Moreover, the use of UDCA, an agent demonstrated to slow the progression of liver disease and improve liver biochemistry in PBC,[29] appears to have no identifiable effect on fatigue severity. These observations would be more supportive of fatigue in PBC resulting from pathological processes to which PBC in some way acts as a co-factor, and to which PBC patients are thus pre-disposed, than it occurring as a direct consequence of liver disease.

The mortality rate for patients who participated in the original fatigue study cohort was 20.6%. Death certificate data were available for all the patients who died during follow-up allowing confirmation of the mortality rate. The annualised mortality rate observed for the current cohort was very similar to that reported by our group for an earlier cohort of North-Eastern UK PBC patients.[20] The apparent differences in mortality rates between the two Newcastle studies and a recent French study [30] are likely to reflect different patient demographics. Survival was significantly lower in patients with high fatigue scores at the study outset, with high FIS being independently associated with reduced survival on multi-variate analysis (the B value on proportional hazards regression for FIS>40 at study outset was 0.91 (p<0.05) indicating that presence of fatigue at the study outset (defined as FIS>40) was independently associated with a relative risk of dying during follow-up of 1.91 compared to the risk in patients in whom fatigue was absent (defined as FIS<40)). The other adverse prognostic indicators at enrolment for the current cohort were age, serum albumin and serum bilirubin (parameters previously well established as markers of adverse prognosis in PBC). These observations suggest that the pathological processes responsible for fatigue expression in PBC are not benign.

In this study cohort cardiac, but not malignant, or directly liver disease-associated deaths were significantly over-represented in the subgroup of patients who had high fatigue severity scores at the outset of the study. There are several potential explanations for the apparent association between fatigue and subsequent cardiac death. The first would be incorrect mode of death assignment. We could find no evidence to support this possibility. Indeed, all cardiac death patients had positive diagnostic findings (ECG features of arrhythmia or myocardial infarction or echo-cardiographic features of heart failure) or post-mortem findings compatible with cardiac cause of death. The difficulties inherent in cause of death assignment particularly in the context of sudden cardiac death secondary to arrhythmia even following post-mortem mean, however, that the possibility of error in cause of death assignment remain. A second potential explanation would be that the high fatigue group at the outset of study contained a proportion of patients with pre-existing atherosclerotic cardiovascular disease or heart failure, or risk factors for the development of such disease (such as diabetes), which pre-disposed to both their fatigue at the time of the study and their subsequent death. The limitations of the original study protocol mean, however, that although the available records confirm that diagnosed heart disease and risk factors for heart disease were absent from the vast majority of the patients who subsequently died of cardiac causes we cannot exclude the possibility that occult heart disease was present in a number of the fatigued patients who died of cardiac causes during follow-up. If this were the case (and future prospective studies addressing cardiac risk together with fatigue assessment in PBC will be required to answer this question) it would have implications for our understanding of fatigue pathogenesis in PBC (implying, as it does, multi-factorial aetiology with the implication that a single agent approach to therapy is less likely to be effective) and would add to the ongoing debate regarding atherosclerotic disease risk in PBC.[31][32]

A third explanation for the apparent links between fatigue in PBC and cardiovascular mortality might be autonomic dysfunction. Our group, and others, have recently identified a high prevalence of abnormalities of autonomic function in PBC patients (including reduced heart-rate variability and blood-pressure instability.[33][34][35][36] Autonomic dysfunction of this type has previously been demonstrated (in the non-liver setting) to be associated with an increased risk of cardiac mortality (including sudden cardiac death).[37][38][39] Furthermore, degree of autonomic dysfunction has previously been demonstrated to show an association with fatigue severity in both PBC [35] and other fatigue associated conditions such as multiple sclerosis,[40] autonomic failure [41] and chronic fatigue syndrome.[42][43][44] One explanation for our findings might therefore be that PBC...
predisposes to autonomic dysfunction which results in fatigue, but which also puts affected patients at risk of cardiac death via mechanisms (such as sudden cardiac death) which may have been under-detected in earlier studies of cardiac risk in PBC which typically focused on atherosclerotic disease.

In this study we have demonstrated that, in PBC patients affected by fatigue (and not all patients and populations are so affected) the symptom is a chronic one with, seemingly, little evidence of spontaneous or therapy-related resolution. This symptom constancy, together with the emerging evidence regarding the degree to which it can impair quality of life, means that further efforts to identify therapies able to ameliorate fatigue in PBC are warranted. Our observations regarding the apparent associations between fatigue, reduced survival, and apparent risk of cardiac-related death add further complexity of our current understanding of the pathogenesis of fatigue in PBC. Further prospective studies in this area are again warranted.

**ACKNOWLEDGEMENTS**
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**Declarations**
None of the authors have any conflict of interest
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FIGURE LEGENDS

Figure 1: a) Distribution of FIS values in 2000 and 2004 in patients surviving to follow-up who were not transplanted during the follow-up period. Mean value is denoted. b) Correlation between individual FIS values in patients in 2000 and 2004. Non-transplanted patients are denoted by closed circles, patients transplanted during follow-up by open circles. Correlation data (with 95% CI) are for the non-transplanted patient group. c) Distribution of FIS values in 2000 and 2004 in patients surviving to follow-up who were transplanted during the follow-up period. Mean value is denoted.

Figure 2: FIS values in 2000 and 2004 for a) Patients not receiving UDCA at any stage of the study. b) Patients who commenced UDCA at a dose of 10-12mg/Kg between 2000 and 2004 and who were still receiving this medication at the time of the follow-up study. c) Patients receiving UDCA at a dose of 10-12mg/Kg throughout the study period.

Figure 3: a) Comparison of the FIS values at the study outset for patients who survived to follow-up and in those who died during follow-up (horizontal bar denoted median value). b) Survival in patients in the 2000 study cohort with fatigue scores above and below 40 (the median score for PBC patients in this cohort).[4]
r=0.74, p<0.0001

p=ns

p<0.005
a) FIS at Study Entry

- FIS < 40 in 2000
- FIS > 40 in 2000

p < 0.05

b) Percentage of Patients Surviving

- FIS < 40 in 2000
- FIS > 40 in 2000

p = 0.006

Months of Follow-Up
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